

## **PRESCRIBING INFORMATION**

### **HAVRIX®**

#### **(Hepatitis A Vaccine, Inactivated)**

#### **DESCRIPTION**

HAVRIX (Hepatitis A Vaccine, Inactivated) is a noninfectious hepatitis A vaccine developed and manufactured by GlaxoSmithKline Biologicals. The virus (strain HM175) is propagated in MRC-5 human diploid cells. After removal of the cell culture medium, the cells are lysed to form a suspension. This suspension is purified through ultrafiltration and gel permeation chromatography procedures. Treatment of this lysate with formalin ensures viral inactivation. HAVRIX contains a sterile suspension of inactivated virus; viral antigen activity is referenced to a standard using an enzyme linked immunosorbent assay (ELISA), and is therefore expressed in terms of ELISA Units (EL.U.).

HAVRIX is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear colorless supernatant may form on storage. After shaking, the vaccine is a slightly turbid white suspension.

Each 1-mL adult dose of vaccine consists of not less than 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of aluminum as aluminum hydroxide.

There are 2 pediatric dose formulations, each with its own dosing schedule (see DOSAGE AND ADMINISTRATION). The formulations are: Not less than 360 EL.U. of viral antigen/0.5 mL; not less than 720 EL.U. of viral antigen/0.5 mL. Each dose is adsorbed onto 0.25 mg of aluminum as aluminum hydroxide.

The vaccine preparations also contain 0.5% (w/v) of 2-phenoxyethanol as a preservative. Other excipients are: Amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). Residual MRC-5 cellular proteins (not more than 5 mcg/mL) and traces of formalin (not more than 0.1 mg/mL) are present. Neomycin sulfate, an aminoglycoside antibiotic, is included in the cell growth media; only trace amounts (not more than 40 ng/mL) remain following purification.

#### **CLINICAL PHARMACOLOGY**

The hepatitis A virus (HAV) belongs to the picornavirus family. Only one serotype of HAV has been described.<sup>1</sup>

Hepatitis A is highly contagious with the predominant mode of transmission being person-to-person via the fecal-oral route. Infection has been shown to be spread (1) by contaminated water or food; (2) by infected food handlers<sup>2</sup>; (3) after breakdown in usual sanitary conditions or after floods or natural disasters; (4) by ingestion of raw or undercooked shellfish (oysters, clams, mussels) from contaminated waters<sup>3</sup>; (5) during travel to areas of the world with poor hygienic conditions<sup>4,5</sup>; (6) among institutionalized children and adults<sup>6</sup>; (7) in day-care

centers where children have not been toilet trained<sup>7</sup>; (8) by parenteral transmission, either blood transfusions or sharing needles with infected people.<sup>1</sup>

The level of economic development influences the prevalence of hepatitis A and the age at which it is most likely to occur. In developing countries with poor hygiene and sanitation, about 90% of children are infected by age 5 years.<sup>1</sup> As conditions improve, the prevalence decreases and the age at which infection occurs increases. Hence it is more likely to occur in adulthood, when disease is generally more severe and more likely to be fatal.<sup>1</sup> In the United States, attack rates for hepatitis A infection are cyclical and vary by population. The rates have increased gradually from 9.2 per 100,000 in 1983 to 14.6 per 100,000 in 1989.<sup>8</sup>

The incubation period for hepatitis A averages 28 days (range: 15 to 50 days).<sup>9</sup> The course of hepatitis A infection is extremely variable, ranging from asymptomatic infection to icteric hepatitis. However, most adults (76% to 97%) become symptomatic.<sup>10</sup> Symptoms range from mild and transient to severe and prolonged and may include fever, nausea, vomiting, and diarrhea in the prodromal phase, followed by jaundice in up to 88% of adults, as well as hepatomegaly and biochemical evidence of hepatocellular damage.<sup>10</sup> Recovery is generally complete and followed by protection against HAV infection. However, illness may be prolonged, and relapse of clinical illness and viral shedding have been described.<sup>11</sup>

Hepatitis A infection is often asymptomatic in children under 2 years of age, who nonetheless excrete the virus in their stool and thereby serve as a source of infection.<sup>10</sup> In older patients and persons with underlying liver disease, it is generally much more severe.<sup>1</sup> This is reflected in mortality rates. While an overall case fatality rate of 0.6% has been reported, a case fatality rate of 2.7% has been reported in patients  $\geq 49$  years of age.<sup>1</sup> Indeed, while 67% of cases occur in children, over 70% of deaths occur in those over the age of 49 years.<sup>1</sup>

There is no chronic carrier state. The virus replicates in the liver and is excreted in bile. The highest concentrations of HAV are found in stools of infected persons during the 2-week period immediately before the onset of jaundice and decline after jaundice appears.<sup>12</sup> Children and infants may shed HAV for longer periods than adults, possibly lasting as long as several weeks after the onset of clinical illness.<sup>13</sup> Chronic shedding of HAV in feces has not been demonstrated, but relapses of hepatitis A can occur in as many as 20% of patients,<sup>1,14</sup> and fecal shedding of HAV may recur at this time.<sup>11</sup>

The presence of antibodies to HAV (anti-HAV) confers protection against hepatitis A infection. However, the lowest titer needed to confer protection has not been determined.

In a chimpanzee challenge study, the quality of protection afforded by immune globulin (IG) prepared from initially seronegative human volunteers vaccinated with HAVRIX was comparable to that afforded by commercial IG. In this experiment, chimpanzees immunized with either preparation developed passive-active immunity when challenged with wild-type HAV. No animal in either group developed clinical illness.

In vitro studies in a randomly selected subset of human subjects (n = 80) showed anti-HAV induced by HAVRIX to have functional activity. This was demonstrated by a neutralization

assay and a competitive inhibition assay using a panel of monoclonal antibodies known to have neutralizing activity.

**Immunogenicity in Adults:** In 3 clinical studies involving over 400 healthy adult volunteers given a single 1440 EL.U. dose of HAVRIX, specific humoral antibodies against HAV were elicited in more than 96% of subjects when measured 1 month after vaccination. By day 15, 80% to 98% of vaccinees had already seroconverted (anti-HAV  $\geq 20$  mIU/mL [the lower limit of antibody measurement by current assay]). Geometric mean titers (GMTs) of seroconverters ranged from 264 to 339 mIU/mL at day 15 and increased to a range of 335 to 637 mIU/mL by 1 month following vaccination.<sup>15</sup>

The GMTs obtained following a single dose of HAVRIX are at least several times higher than that expected following receipt of IG.

In a clinical study using 2.5 to 5 times the standard dose of IG (standard dose = 0.02 to 0.06 mL/kg), the GMT in recipients was 146 mIU/mL at 5 days post-administration, 77 mIU/mL at month 1, and 63 mIU/mL at month 2.<sup>15</sup>

In 2 clinical trials in which a booster dose of 1440 EL.U. was given 6 months following the initial dose, 100% of vaccinees (n = 269) were seropositive 1 month after the booster dose, with GMTs ranging from 3,318 mIU/mL to 5,925 mIU/mL. The titers obtained from this additional dose approximate those observed several years after natural infection.

In a subset of vaccinees (n = 89), a single dose of HAVRIX 1440 EL.U. elicited specific anti-HAV neutralizing antibodies in more than 94% of vaccinees when measured 1 month after vaccination. These neutralizing antibodies persisted until month 6. One hundred percent of vaccinees had neutralizing antibodies when measured 1 month after a booster dose given at month 6.

Immunogenicity of HAVRIX was studied in subjects with chronic liver disease of various etiologies. 189 healthy adults and 220 adults with either chronic hepatitis B (n = 46), chronic hepatitis C (n = 104), or moderate chronic liver disease of other etiology (n = 70) were vaccinated with HAVRIX 1440 EL.U. on a 0- and 6-month schedule. The last group consisted of alcoholic cirrhosis (n = 17), autoimmune hepatitis (n = 10), chronic hepatitis/cryptogenic cirrhosis (n = 9), hemochromatosis (n = 2), primary biliary cirrhosis (n = 15), primary sclerosing cholangitis (n = 4), and unspecified (n = 13). At each time point, GMTs were lower for subjects with chronic liver disease than for healthy subjects. At month 7, the GMTs ranged from 478 mIU/mL (chronic hepatitis C) to 1,245 mIU/mL (healthy), as determined by a commercial ELISA. The relevance of these data to the duration of protection afforded by HAVRIX is unknown. One month after the first dose, seroconversion rates in adults with chronic liver disease were lower than in healthy adults. However, 1 month after the booster dose at month 6, seroconversion rates were similar in all groups; rates ranged from 94.7% to 98.1%.

**Immunogenicity in Children and Adolescents:** In 6 clinical studies involving pediatric vaccinees (n = 762) ranging from 1 to 18 years of age, the GMT following 2 doses of HAVRIX 360 EL.U. given 1 month apart ranged from 197 to 660 mIU/mL. Ninety-nine percent of subjects seroconverted following 2 doses. When a booster (third) dose of HAVRIX 360 EL.U. was

administered 6 months following the initial dose, all subjects were seropositive 1 month following the booster dose, with GMTs rising to a range of 3,388 to 4,643 mIU/mL. In 1 study in which children were followed for an additional 6 months, all subjects remained seropositive. Solicited adverse effects were similar in frequency and nature to those seen following administration of ENGERIX-B® [Hepatitis B Vaccine (Recombinant)].

In 4 clinical studies, children and adolescents (n = 314), ranging from 2 to 19 years of age, were immunized with 2 doses of HAVRIX 720 EL.U./0.5 mL given 6 months apart. One month after the first dose, seroconversion ranged from 96.8% to 100%, with GMTs of 194 mIU/mL to 305 mIU/mL. In studies in which sera were obtained 2 weeks following the initial dose, seroconversion ranged from 91.6% to 96.1%. One month following a booster dose at month 6, all subjects were seropositive, with GMTs ranging from 2,495 mIU/mL to 3,644 mIU/mL.<sup>15</sup>

In 1 additional study in which the booster dose was delayed until 1 year following the initial dose, 95.2% of the subjects were seropositive just prior to administration of the booster dose. One month later, all subjects were seropositive, with a GMT of 2,657 mIU/mL.<sup>15</sup>

Also, HAVRIX has been found to be highly efficacious in a clinical study of children at high risk of HAV infection (see below).

At present, the duration of protection afforded by HAVRIX has not been established. Therefore it is unknown if the protection provided to immunized children will last until adulthood.

**Protective Efficacy:** Protective efficacy with HAVRIX has been demonstrated in a double-blind, randomized controlled study in school children (age 1 to 16 years) in Thailand who were at high risk of HAV infection. A total of 40,119 children were randomized to be vaccinated with either HAVRIX 360 EL.U. or ENGERIX-B at 0, 1, and 12 months. 19,037 children received a primary course (0 and 1 months) of HAVRIX and 19,120 children received a primary course (0 and 1 months) of ENGERIX-B. 38,157 children entered surveillance at day 138 and were observed for an additional 8 months. Using the protocol-defined endpoint ( $\geq 2$  days absence from school, ALT level  $>45$  U/mL, and a positive result in the HAVAB-M test), 32 cases of clinical hepatitis A occurred in the control group; in the HAVRIX group, 2 cases were identified. These 2 cases were mild both in terms of biochemical and clinical indices of hepatitis A disease. Thus the calculated efficacy rate for prevention of clinical hepatitis A was 94% (95% confidence intervals 74% to 98%).<sup>16</sup>

In outbreak investigations occurring in the trial, 26 clinical cases of hepatitis A (of a total of 34 occurring in the trial) occurred. No cases occurred in HAVRIX vaccinees.

Using additional virological and serological analyses post hoc, the efficacy of HAVRIX was confirmed. Up to 3 additional cases of very mild clinical illness may have occurred in vaccinees. Using available testing, these illnesses could neither be proven nor disproven to have been caused by HAV. By including these as cases, the calculated efficacy rate for prevention of clinical hepatitis A would be 84% (95% confidence intervals 60% to 94%).

In a study designed to interrupt an epidemic of hepatitis A among Native Americans in Alaska, vaccination with a single dose of HAVRIX (1440 EL.U./mL in adults, 720 EL.U./0.5 mL in children and adolescents) appeared to be efficacious.<sup>17</sup>

## INDICATIONS AND USAGE

HAVRIX is indicated for active immunization of persons  $\geq 2$  years of age against disease caused by hepatitis A virus (HAV).

HAVRIX will not prevent hepatitis caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus, or other pathogens known to infect the liver.

Immunization with HAVRIX is indicated for those people desiring protection against hepatitis A. Primary immunization should be completed at least 2 weeks prior to expected exposure to HAV. Individuals who are, or will be, at increased risk of infection by HAV include:

- *Travelers:* Persons traveling to areas of higher endemicity for hepatitis A. These areas include, but are not limited to, Africa, Asia (except Japan), the Mediterranean basin, eastern Europe, the Middle East, Central and South America, Mexico, and parts of the Caribbean. Current CDC advisories should be consulted with regard to specific locales.
- *Military Personnel*
- *People Living in, or Relocating to, Areas of High Endemicity*
- *Certain Ethnic and Geographic Populations That Experience Cyclic Hepatitis A Epidemics*, such as: Native peoples of Alaska and the Americas.
- *People With Chronic Liver Disease*, including:
  - Alcoholic cirrhosis
  - Chronic hepatitis B
  - Chronic hepatitis C
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
- *Others:*
  - Persons engaging in high-risk sexual activity (such as men having sex with men)<sup>18</sup>
  - Residents of a community experiencing an outbreak of hepatitis A
  - Users of illicit injectable drugs
  - Persons who have clotting factor disorders (hemophiliacs and other recipients of therapeutic blood products). Hepatitis A transmission has been documented in persons with clotting disorders. Susceptible persons in this category, especially those who receive solvent detergent–treated clotting factor concentrates, should be vaccinated against hepatitis A<sup>19</sup> (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).
  - Although the epidemiology of hepatitis A does not permit the identification of other specific populations at high risk of disease, outbreaks of hepatitis A or exposure to hepatitis A virus have been described in a variety of populations in which HAVRIX may be useful:
    - Certain institutional workers (e.g., caretakers for the developmentally challenged)
    - Employees of child day-care centers

- Laboratory workers who handle live hepatitis A virus
- Handlers of primate animals that may be harboring HAV
- *People Exposed to Hepatitis A:*  
 For those requiring both immediate and long-term protection, HAVRIX may be administered concomitantly with IG.  
 The Advisory Committee on Immunization Practices (ACIP) has issued the following recommendations regarding food handlers: “Persons who work as food handlers can contract hepatitis A and potentially transmit HAV to others. To decrease the frequency of evaluations of food handlers with hepatitis A and the need for postexposure prophylaxis of patrons, consideration may be given to vaccination of employees who work in areas where state and local health authorities or private employers determine that such vaccination is cost-effective.”<sup>19</sup>

## CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including neomycin, is a contraindication (see DESCRIPTION). This vaccine is contraindicated in patients with previous hypersensitivity to any hepatitis A-containing vaccine.

## WARNINGS

There have been rare reports of anaphylaxis/anaphylactoid reactions following commercial use of the vaccine.

The vial stopper is latex-free. The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

Hepatitis A has a relatively long incubation period (15 to 50 days). Hepatitis A vaccine may not prevent hepatitis A infection in individuals who have an unrecognized hepatitis A infection at the time of vaccination. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers (although the lowest titer needed to confer protection has not been determined).

## PRECAUTIONS

**General:** As with any parenteral vaccine, epinephrine should be available for use in case of anaphylaxis or anaphylactoid reaction.

As with any vaccine, administration of HAVRIX should be delayed, if possible, in people with any febrile illness, except when, in the opinion of the physician, withholding vaccine entails the greater risk.

HAVRIX should be administered with caution to people with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

As with any vaccine, if administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected immune response may not be obtained.<sup>20</sup>

Care is to be taken by the healthcare provider for the safe and effective use of HAVRIX.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines.

A separate sterile syringe and needle (for single-dose vial) or a sterile disposable unit (prefilled syringe) must be used for each patient to prevent the transmission of infectious agents from person to person. Needles should not be recapped and should be properly disposed.

Special care should be taken to ensure that HAVRIX is not injected into a blood vessel.

**Information for Patients:** Patients, parents, or guardians should be fully informed of the benefits and risks of immunization with HAVRIX.

HAVRIX is indicated in a variety of situations (see INDICATIONS AND USAGE). For persons traveling to endemic or epidemic areas, current CDC advisories should be consulted with regard to specific locales.

Travelers should take all necessary precautions to avoid contact with or ingestion of contaminated food or water.

The duration of immunity following a complete schedule of immunization with HAVRIX has not been established.

**Drug Interactions:** Preliminary results suggest that the concomitant administration of a wide variety of other vaccines is unlikely to interfere with the immune response to HAVRIX.

As with other intramuscular injections, HAVRIX should be given with caution to individuals on anticoagulant therapy.

When concomitant administration of other vaccines or IG is required, they should be given with different syringes and at different injection sites.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** HAVRIX has not been evaluated for its carcinogenic potential, mutagenic potential, or potential for impairment of fertility.

**Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with HAVRIX. It is also not known whether HAVRIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HAVRIX should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** It is not known whether HAVRIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HAVRIX is administered to a nursing woman.

**Pediatric Use:** HAVRIX is well tolerated and highly immunogenic and effective in children  $\geq 2$  years of age. (See CLINICAL PHARMACOLOGY for immunogenicity and efficacy data. See DOSAGE AND ADMINISTRATION for recommended dosage.)

**Geriatric Use:** Clinical studies of HAVRIX did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in overall safety between these subjects and younger adult subjects.

## ADVERSE REACTIONS

During clinical trials involving more than 31,000 individuals receiving doses ranging from 360 EL.U. to 1440 EL.U. and during extensive postmarketing experience in Europe, HAVRIX has been generally well tolerated. As with all pharmaceuticals, however, it is possible that expanded commercial use of the vaccine could reveal rare adverse events not observed in clinical studies.

The frequency of solicited adverse events tended to decrease with successive doses of HAVRIX. Most events reported were considered by the subjects as mild and did not last for more than 24 hours.

Of solicited adverse events in clinical trials, the most frequently reported by volunteers was injection-site soreness (56% of adults and 21% of children); however, less than 0.5% of soreness was reported as severe. Headache was reported by 14% of adults and less than 9% of children. Other solicited and unsolicited events occurring during clinical trials are listed below:

### **Incidence 1% to 10% of Injections:**

*Local Reactions at Injection Site:* Induration, redness, swelling.

*Body as a Whole:* Fatigue, fever ( $>37.5^{\circ}\text{C}$ ), malaise.

*Gastrointestinal:* Anorexia, nausea.

### **Incidence <1% of Injections:**

*Local Reaction at Injection Site:* Hematoma.

*Dermatologic:* Pruritus, rash, urticaria.

*Respiratory:* Pharyngitis, other upper respiratory tract infections.

*Gastrointestinal:* Abdominal pain, diarrhea, dysgeusia, vomiting.

*Musculoskeletal:* Arthralgia, elevation of creatine phosphokinase, myalgia.

*Hematologic:* Lymphadenopathy.

*Central Nervous System:* Hypertonic episode, insomnia, photophobia, vertigo.

**Additional Safety Data:** Safety data were obtained from 2 additional sources in which large populations were vaccinated. In an outbreak setting in which 4,930 individuals were immunized with a single dose of either 720 EL.U. or 1440 EL.U. of HAVRIX, the vaccine was well tolerated and no serious adverse events due to vaccination were reported. Overall, less than 10% of vaccinees reported solicited general adverse events following the vaccine. The most common solicited local adverse event was pain at the injection site, reported in 22.3% of subjects at 24 hours and decreasing to 2.4% by 72 hours. In a field efficacy trial, 19,037 children received the 360 EL.U. dose of HAVRIX. The most commonly reported adverse events following administration of HAVRIX were injection-site pain (9.5%) and tenderness (8.1%), which were reported following first doses of HAVRIX. Other adverse events were infrequent and comparable to the control vaccine ENGERIX-B. Additionally, no serious adverse events due to the vaccine were reported. The large trial further allowed for analysis of rare adverse events, including hospitalization and death. No significant differences were found between the cohorts.

In subjects with chronic liver disease, HAVRIX was safe and well tolerated. Local injection site reactions were similar among all 4 groups, and no serious adverse reactions attributed to the vaccine were reported in subjects with chronic liver disease.

**Postmarketing Reports:** Rare voluntary reports of adverse events in people receiving HAVRIX that have been reported since market introduction of the vaccine include the following:

**Local:** Localized edema.

While no causal relationship has been established, the following rare events have been reported:

**Body as a Whole:** Anaphylaxis/anaphylactoid reactions, somnolence.

**Cardiovascular:** Syncope.

**Hepatobiliary:** Jaundice, hepatitis.

**Dermatologic:** Erythema multiforme, hyperhidrosis, angioedema.

**Respiratory:** Dyspnea.

**Hematologic:** Lymphadenopathy.

**Central Nervous System:** Convulsions, encephalopathy, dizziness, neuropathy, myelitis, paresthesia, Guillain-Barré syndrome, multiple sclerosis.

**Other:** Congenital abnormality.

**Reporting of Adverse Events:** The US Department of Health and Human Services has established the Vaccine Adverse Events Reporting System (VAERS) to accept reports of suspected adverse events after the administration of any vaccine, including, but not limited to, the reporting of events required by the National Childhood Vaccine Injury Act of 1986. The toll-free number for VAERS forms and information is 1-800-822-7967.<sup>21</sup>

## DOSAGE AND ADMINISTRATION

HAVRIX should be administered by intramuscular injection. *Do not inject intravenously, intradermally, or subcutaneously.* In adults, the injection should be given in the deltoid region. HAVRIX should not be administered in the gluteal region; such injections may result in suboptimal response.

HAVRIX may be administered concomitantly with IG, although the ultimate antibody titer obtained is likely to be lower than when the vaccine is given alone. HAVRIX has been administered simultaneously with ENGERIX-B without interference with their respective immune responses.

For individuals with clotting factor disorders at risk of hematoma formation following intramuscular injection, the ACIP recommends that when any intramuscular vaccine is indicated for such patients, “. . . the vaccine should be administered intramuscularly if, in the opinion of a physician familiar with the patient’s bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccinations can be scheduled shortly after such therapy is administered. A fine needle ( $\leq 23$  gauge) should be used for the vaccination and firm pressure applied to the site,

without rubbing, for  $\geq 2$  minutes. The patient or family should be instructed concerning the risk for hematoma from the injection.”<sup>22</sup>

When concomitant administration of other vaccines or IG is required, they should be given with different syringes and at different injection sites.

**Preparation for Administration:** Shake vial or syringe well before withdrawal and use.

Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration. With thorough agitation, HAVRIX is a slightly turbid white suspension.

Discard if it appears otherwise.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used. After removal of the appropriate volume from a single-dose vial, any vaccine remaining in the vial should be discarded.

Primary immunization for adults consists of a single dose of 1440 EL.U. in 1 mL. Primary immunization for children and adolescents (2 through 18 years of age) may follow either of these 2 schedules:

Group	Dose	Schedule
Children and adolescents (2 through 18 years of age)	Primary course: 360 EL.U./0.5 mL	two doses, given 1 month apart (month 0 and month 1)
	Booster: 360 EL.U./0.5 mL	6 to 12 months after primary course
	<b>OR</b>	
	Primary course: 720 EL.U./0.5 mL	one dose (month 0)
	Booster: 720 EL.U./0.5 mL	6 to 12 months after primary course

Individuals should not be alternated between the 360 EL.U. and 720 EL.U. doses. Those who receive an initial 360 EL.U. dose should continue on the 360 EL.U. dosing schedule. Likewise, those individuals who receive a single 720 EL.U. primary dose should receive a 720 EL.U. booster dose.

For all age groups, a booster dose is recommended anytime between 6 and 12 months after the initiation of the primary dose in order to ensure the highest antibody titers.

In those with an impaired immune system, adequate anti-HAV response may not be obtained after the primary immunization course. Such patients may therefore require administration of additional doses of vaccine.

## STORAGE

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen. Do not dilute to administer.

## HOW SUPPLIED

HAVRIX is supplied as a slightly turbid white suspension in vials and prefilled TIP-LOK<sup>®</sup> syringes.

360 EL.U./0.5 mL in Single-Dose Vials

NDC 58160-836-01 Package of 1

720 EL.U./0.5 mL in Single-Dose Vials and Prefilled Syringes

NDC 58160-837-01 Package of 1 Single-Dose Vial

NDC 58160-837-11 Package of 10 Single-Dose Vials

NDC 58160-837-46 Package of 5 Prefilled Disposable TIP-LOK Syringes (packaged without needles)

NDC 58160-837-50 Package of 25 Prefilled Disposable TIP-LOK Syringes (packaged without needles)

1440 EL.U./mL in Single-Dose Vials and Prefilled Syringes

NDC 58160-835-01 Package of 1 Single-Dose Vial

NDC 58160-835-41 Package of 1 Prefilled Disposable TIP-LOK Syringe (packaged without needle)

NDC 58160-835-46 Package of 5 Prefilled Disposable TIP-LOK Syringes (packaged without needles)

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